ORIGINAL ARTICLE

Framework for the Use of Biological Medicines in South-Africa

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ABSTRACT

Background: The use of Biological Medicines has grown worldwide and is aimed at improving the quality of life of patients. However, in South Africa access to Biological Medicines remains limited. Therefor the aim of the study was to develop a framework for the use of Biological Medicines in South Africa.

Objective: To develop a framework for the use of BM's in South-Africa via the Delphi method

Methods: Using a team of experts on Biological Medicines to evaluate and integrate the opinions from the three stakeholders (i.e., the young doctors, prescribing specialists, and patients) by the Delphi method, a framework for the use of Biological Medicines in South-Africa was developed

Results: In the Delphi questionnaire study, there were 15 panel members that responded out of 20 who received the invitation. The framework proposes that appropriate use of Biological Medicines requires establishment of 'guidelines for use of Biological Medicines' but only after successful implementation of the following five factors:

1. Ensuring appropriate training of health professionals (medical practitioners and specialists) on Biological Medicines by revising the training syllabus to improve coverage on Biological Medicines.
2. Improved coverage and availability of study resources on biological medicines
3. Improving the availability of Biological Medicines to clinicians who need to use them.
4. Promoting appropriate patient information to ensure compliance and timely response in case of problems.
5. Promoting a well-informed community about Biological Medicines, with the aim of improving appropriate patient support and pharmacovigilance on Biological Medicines.

Discussion: Adapting the elements of the framework will address the challenges we face regarding ease of access and rational use of Biological Medicines.

Conclusion: There is a definite need for this framework to become a reality. Adapting the elements of the framework will address the challenges of Biological medicines regarding appropriate training, information resources.

Keywords: Biological medicine; Framework

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INTRODUCTION

Biological medicines (BM) are therapeutic substances (monoclonal antibodies, cytokines, peptides, etc.), derived from biological sources that are used to treat, diagnose or prevent disease. Over the past two decades, there has been an increased use of BM owing to their effectiveness in a wide variety of chronic diseases such as autoimmune disorders, intractable cancers, cardiovascular diseases and allergy [1,2]. Unfortunately, the use of BM has not been without challenges [3,4].

The response to BM is influenced by many factors which include, to mention but a few, disease activity and severity, cytokine levels, immune cell genotype and phenotypes, and presence of autoantibodies, and this is in addition to the patient characteristics such as gender, age, body mass index and the concomitant use of other drugs [5]. Their use is also limited by the heightened fear for host rejection and/or tolerance, which can exhibit, respectively, as hypersensitivity (immune) reactions and failure of response due to drug antibodies. Some BM requires preliminary screening tests because they only work in patients who express specific endogenous structures such as receptors or cell-subclasses or genotype. *Trastuzumab* acts on tumours expressing *HER-2* receptors, while *rituximab* is more effective in B-cells with the *CD20* protein, and *natalizumab* inhibition of *α4-integrin* is best in endothelial cells expressing the vascular cell adhesion molecule 1 (*VCAM-1*) gene. Also, because most BM is targeted at interfering with the physiological actions of their respective endogenous compounds, they may predispose patients to related adverse events. For instance, *infliximab* inhibits *TNF-α* which is required for normal inflammation and other processes, leading to infections as a complication. As such, these BM require continuous testing to monitor response and safety during therapy [3,4], and this makes them more costly, particularly with the additional tedious procurement requirements and designation to particular prescribers [6-8]. Furthermore, the side-effects profile of BM does not fit into the current pharmaceutical medicines' adverse drug reaction (ADR) paradigm [2]. Whereas the ADR of pharmaceutical medicines are classified into 5 types (A, B, C, D and E), those of BM are differently classified into 5 new types (α, β, γ, δ and ε). Therefore, appropriate use of BM requires a clinician with adequate knowledge on the selection of suitable patients to ensure maximum benefit, and avoiding high-risk groups in order to reduce the risk of adverse events [6]. This includes appropriate training not only on the pharmacology of BM, but also on the population factors that determine response and safety of BM [9,10]. Such knowledge would empower clinicians to identify the major determinants of response and toxicity of BM in the local South African patient population, to enable appropriate modifications in the guidelines for the use of BM in our patients. Unfortunately, this information (knowledge) is still not generally available in standard textbooks or general literature, hence is not accessible to most clinicians. Worse still, in South Africa, prescribing of BM is limited to specific specialists in central hospitals who, unfortunately, are not in reach of all patients that need them. As such, there was a need to investigate the factors that influence the utilization of BM in South Africa.

This study is an accumulation of our previous findings that were established. The previous studies confirmed the factors affecting the utilisation of Biological Medicines in the Free State. This includes surveys for newly qualified doctors, specialist prescribing BM's as well as Patients using BM's.

Eleven concerns were identified from the newly qualified doctors survey, twenty-two concerns from the Specialist prescribing BM's survey and sixteen concerns from patients who received Biological Medicines, these concerns were used to develop a framework to guide the use of Biological Medicines in South-Africa. The diagram below is a culmination of our previous findings. The previous studies established

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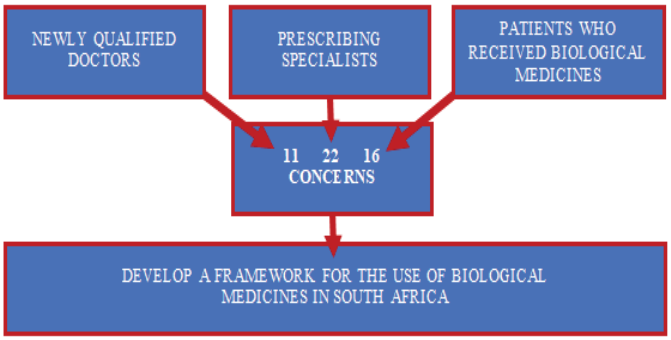

Figure 1: Factors affecting the utilization of biological medicines in the Free State.

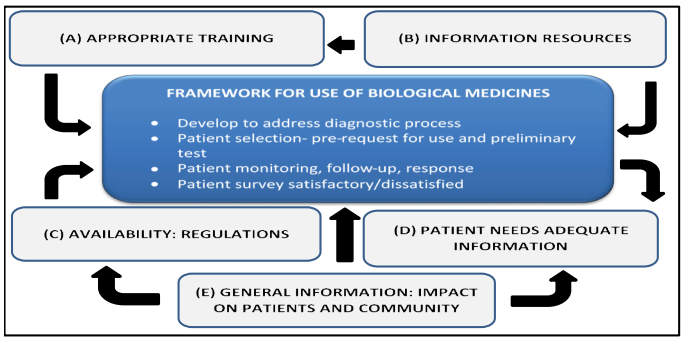

Figure 2: Framework for the use of biological medicines in South-Africa.

what factors affect the utilisation of Biological Medicines in the Free State shown in Figure 1.

A Delphi questionnaire was successfully used to obtain the opinions of a panel of experts on the different aspects of Biological Medicines in South Africa that were identified by the young doctors, prescribers and patients. These opinions were used to draft the South African proposal framework for the use of Biological Medicines.

METHODOLOGY

The Delphi method is a way of collecting expert point of views on a specific topic. It is a critical step in the development of the questionnaire that is based on a series of questions to the panellists for rating and evaluation.

The objective of this study was to develop a framework to guide the use of Biological Medicines in South-Africa via the Delphi method.

The University of the Free State Health Sciences Research Ethics Committee (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee granted ethical approval.

Factors affecting the use of Biological Medicines were pin-pointed and divided into 4 major categories:

- Section A: Use of BM, How to prescribe Biological Medicines
- Section B: Information resources
- Section C: Patient care and management
- Section D: Availability, prescription, dispensing and procurement

The Delphi questionnaire addressed the major concerns based on the factors affecting the use of Biological Medicines.

The selection of an expert panel

Consist of 20 Experts from different disciplines. All had extensive knowledge & experience regarding Biological Medicines. Specialists in the following fields participated: *Oncology, Hematology, Gastro-enterology*, Rheumatology, as well as Biological Medicine, Internal Medicine, Pharmaceutical Sciences, Medical regulation and Medical Microbiology.

The panel included international experts on Biological Medicines as well as members of the Medicine Control Council, Biological Medicines Committee and Central Clinical Committee. These experts were selected by means of a coding system.

The Delphi procedure consists of a consent form and letters of invitation sent to 20 members of the expert panel. The expert accepted invitation and returned signed consent form via email to the researcher. Round 1 of the Delphi questionnaire was sent to the experts by e-mail and the responses were integrated and analysed, where they appeared equal. Round 2 of the Delphi questionnaire was reformulated according to the expert responses or suggestions; integrated to eliminate those on which they agreed. Round 3 is done the same as round 2. Round 4 is done the same as round 3, until consensus was reached.

The Delphi questionnaire was sent to the experts by e-mail; this was called Round 1 of the survey. Round 1 of the questionnaire consisted of 30 statements on the use of BM's in South-Africa with 57% consensus rate. Round 2 consisted of 13 of the remaining statements and 5 newly added statements. Consensus was reached in Round 2. A framework for the use of Biological Medicine in South-Africa was drafted after consensus was reached.

Statistical analysis

DATA was captured on an excel data sheet. A coding system was used to track respondents and their responses from the first to the second round

RESULTS

Out of the 20 experts identified, 75% completed the questionnaire (Figure 2). The team included 60% (n=12) males, and 40% (n=8) females. The framework consisted of 5 division, firstly appropriate training, secondly information resources, then the availability regulations, and patient require adequate information and finally the general information, impact on patient and community. The framework for the use of Biological Medicines was developed to address the diagnostic process:

- Patient selection- pre-request for use and preliminary test
- Patient monitoring, follow-up, response as well as
- Patient survey satisfactory or dissatisfied

Appropriate training

It focuses on undergraduate and postgraduate (Specialists) programmes and refer to following up on patients and providing patient information to students, manage patients and drawing up of guidelines for Biological Medicine use.

Information resources

Pharmacology of biological medicines must be covered well in standard medical textbooks, and used for seminars, continuing medical education programme and expert groups.

Biological medicines must not be the last resort

There should be more approved Biological Medicines on the market; the government should improve funding; it should be added to the standard medicine code list of Department of Health; it should be administered in time for the patient to benefit.

Patients require adequate knowledge to improve compliance

To know what to do when they experience side-effects; and to guide them when there is a religious or cultural objection.

General information and impact on patients and community

Patient support in the form of travel assistance and funds for Biological medicines and advocacy group improvement is required.

DISCUSSION

There is a definite need for this framework to become a reality. Adapting the elements of the framework will address the challenges we face regarding ease of access and rational use of Biological Medicines. The provision of information resources of Biological Medicines is limited; therefore information of Biological Medicines is not adequately covered in medical textbooks - compared to the information that is available on pharmaceutical agents. There is a need to develop a modified training curriculum that includes information on Biological medicines to meet the needs of patients and prescribers. Improved knowledge of Biological Medicine leads to improved care of patients on these agents; therefore, the doctors will be better equipped to serve the community.

There are a number of publications that characterize the pharmacokinetics and pharmacodynamics of monoclonal antibodies in Asian versus non-Asian populations, and the biological effects of cytokines in Chinese and non-Chinese patients [8,9], but no similar studies have been done in South Africa.

The appropriate utilisation of any BM requires adequate knowledge of not only their pharmacology, but also factors that determine appropriate response and safety [7-9]. It is therefore of utmost importance for a clinician to take all available information into consideration before prescribing BM in order for his/her patients to fully benefit [10]. Unfortunately, as supported by findings of this study, information and guidelines on BM is still not generally available in standard textbooks or literature [2].

Improved knowledge of Biological Medicines leads to improved care of patients on these agents; therefore, the doctors will be better equipped to serve the community. A major strength was the cross-sectional study design that was used to prove assumptions.

Limitations of the study was the deadline of the Delphi questionnaires due to the fact that experts were used to complete the questionnaire, they had busy programs and did not observe. Another limitation was stay in the timeframe; due to the fact that questionnaires were used, it took a lot of energy and was time consuming to receive it back. Future studies can benefit to learn more about the adverse effects of BM in a specific population and support the young doctors in the form of guidelines on the use of BM. The survey provides a baseline of the knowledge level of newly qualified doctors; a suggestion is that a similar survey will be repeated in two years' time to monitor the changes.

CONCLUSION

Biological Medicines are improving the quality of life of patients. Therefore, support was offered in the form of a framework to ensure that current patients benefit.

DECLARATIONS

Abbreviations

ADR: Adverse drug reaction, BM: Biological Medicines, HSREC: Health Sciences Research Ethics Committee.

Ethics approval and consent to participate

The University of the Free State Health Sciences Research Ethics Committee (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee granted ethical approval. Newly qualified doctors give their consent before they completed the questionnaire.

COMPETING INTEREST

The authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTIONS

Dr. M. Mocke-Richter collected and analysed the data and wrote the article with support of Prof. A. Walubo. Prof A. Walubo provided critical feedback and helped shape the research analysis, and manuscript. The authors have read and approved the final version of the article.

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